OpenFoodTox and Tools for Chemical Risk Assessment at EFSA

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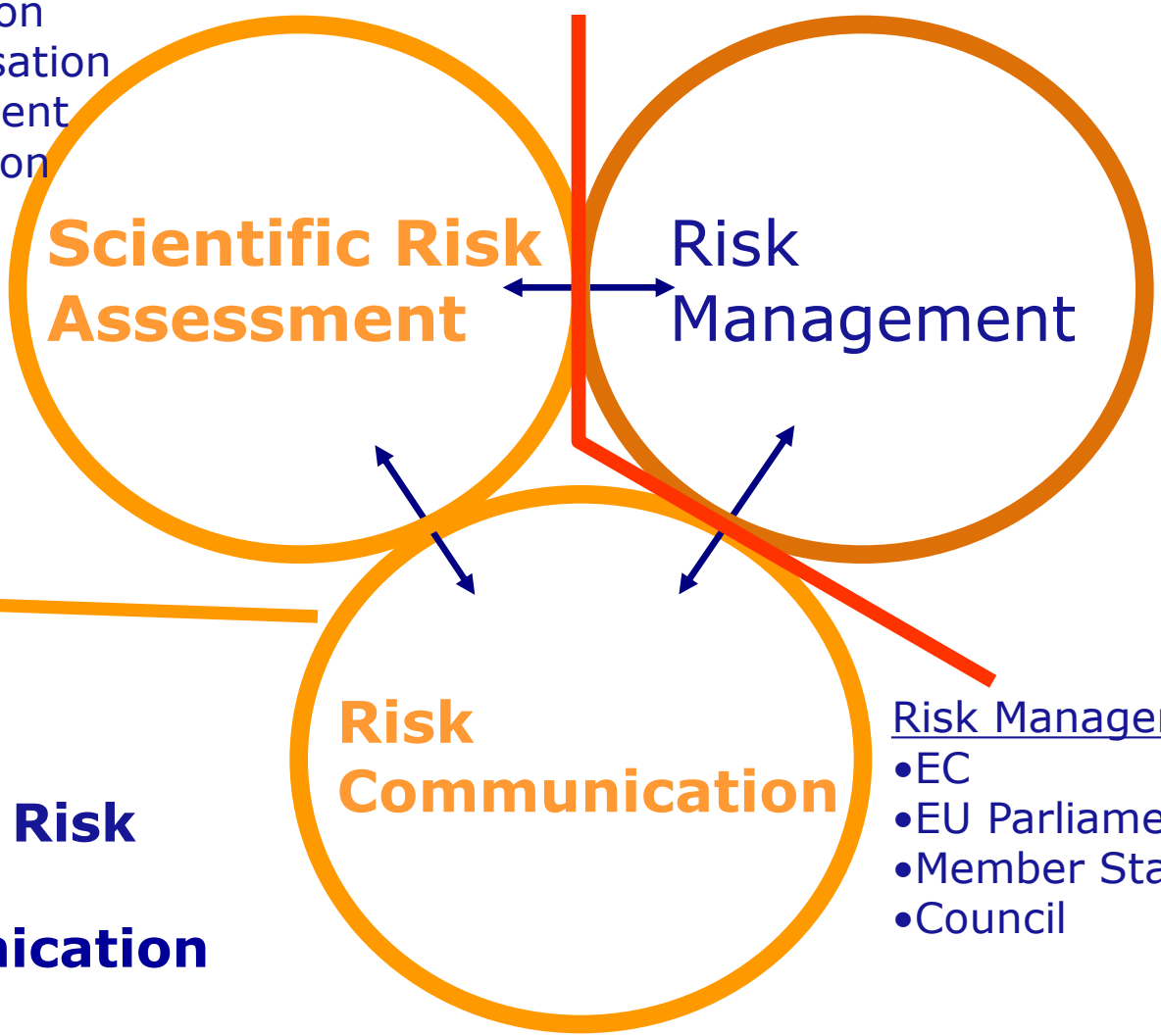
efsa
European Food Safety Authority

EFSA's Role in Risk Analysis

Methodology Codex Alimentarius:

- Hazard identification
- Hazard characterisation
- Exposure assessment
- Risk characterisation



EFSA

- **Independent Risk Assessment**
- **Risk communication**

Risk Manager

- EC
- EU Parliament
- Member States
- Council

FROM QUESTION TO ANSWER

European Commission

European Parliament

Member States

EFSA ("self mandate")

Question?

Terms of reference

Background

Risk Assessment

Opinion

Risk Management

Consumers

Media

Industry

Professionals

Risk Communication

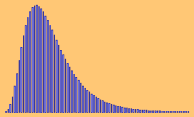
Principles of Chemical Risk Assessment

STEPS IN CHEMICAL RISK ASSESSMENT

Exposure assessment

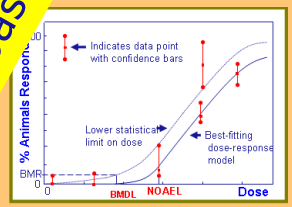
Occurrence of chemicals
in food, feed, water, environmental media
X
Food consumption

Deterministic vs probabilistic



Hazard Identification
Hazard Characterisation

Toxicokinetics (ADME)
Toxicity: Genotox,acute/sub-chronic/chronic toxicity,
NOELs, BMDL, LOAELs (animal, hum)
NOEC, PNECs (Ecology..)
Health based Guidance Value
(ADI, TDI…)



EFSA's Chemical Hazard Database

Risk Characterisation

Exposure and Hazard
Humans: Health-based guidance values vs ex ure
Margin of Exposure (genotox carcinogens)
Margin of safety (animal)
Environmental standards (ecological),

DATA/EVIDENCE AVAILABLE IN CHEMICAL RA

Tier	Exposure Assessment		Hazard identification		Hazard characterisation		Risk Characterisation
	Occurence	**Consumption**	**TK**	**TD**	**TK**	**TD**	
0	Semi-Q	Default values	No data	No data	*in silico* Read across	Default values TTC Read across *In silico* Default UF	e.g. Default values Qualitative
1	Point estimates	Point estimates in food categories	*In silico* Limited data Semi-Q	*In silico* Limited data Read across	*in silico* Basic TK Read across	*in silico* Read across NOAEL Default UF	e.g. Semi-quantitative
2	Measured data	Measured in some food categories	Dossier data Qttve	Dossier Data	*in silico* ADME data	NOAEL/ BMDL Default *in silico* UF	e.g. Quantitative Deterministic/ Probabilistic
3	Large measured dataset	Full patterns - food categories	Dossier and/or lit. (*in vitro*, *in vivo*)	Data in dossier and/or lit. (*in vitro*, OMICs, epi)	MoA/AOP, Epi data, PB-PK model, BBDR, BMDL Chemical specific adjustment factor (CSAF)		e.g. Quantitative Full probabilistic

EFSA' S CHEMICAL HAZARDS DATABASE: OPENFOODTOX

- **Catalogue of EFSA's chemical toxicity data since creation**

  -Contaminants (Human and Animal health)

  -Vitamins and minerals (Human health) (NDA),

  -Food additives and Nutrient Sources, Food contact materials, Flavourings and processing aids ,enzymes (Human Health)

  -Feed Additives (Human and Animal Health, Ecotoxicology)

  -Pesticides (Human and Animal health, Ecotoxicology)

- **Easy Reference and Crisis**

  -One reference Database on Chemical Hazards: Search easily and efficiently

  -Crisis: Quick and Easy access to all EFSA's Hazard Data

- **International Harmonisation**

  -International efforts:Harmonise Templates for Hazard Data (ECHA/OECD)

  -Data Model based on templates compatible with IUCLID/ ECHA-OECD QSAR toolbox

WHAT DOES OPENFOODTOX CONTAIN ?

- **Chemical Information**

Information on chemical nomenclature (EU nomenclature, IUPAC, CAS...), trade name, chemical group/panel (i.e. pesticide), chemical use (i.e fungicide), chemical structure (i.e triazoles, organophosphates….).

- **Document descriptors**

Information on EFSA's opinion for the specific chemical or group of chemicals. Info from EFSA 's RAW system (question number, mandate, number), link to the document

- **Toxicity Endpoint/ Hazard identification**

Information on critical toxicity study using OECD picklists when possible (species, dose, target organ…)

- **Critical study to demonstrate genotoxicity status**

Providing essential information of critical genotoxicity study when assessed

- **Hazard /Risk characterisation**

Information for health based guidance values (ADI/TDI), margin of exposures, safety factors…

CONTENT

1,479 Scientific outputs (metadata + DOI)

11,818 risk assessment summaries

4,185 Substances (chemical identifiers including SMILES)

8,400 Toxicological endpoint studies

133 Positive genotoxicity studies

OPENFOODTOX AND IN SILICO TOOLS

- OpenFoodTox in EFSA Data Warehouse (editorial in prep) and OECD E-chem portal since April 2016
- Illustrate the use of OpenFoodTOx in different areas of chemical RA through review articles with EFSA units
- Explore Case studies to develop *in silico* tools : acute contact toxicity pesticides bees QSRA models
- Read Across in toxicology combined with Toxicokinetic data
- Risk assessment of mixtures: case studies

Modern Methods in Chemical RRisk Assessment

European Food Safety Authority

EFSA Journal 2014;12(4):3638

SCIENTIFIC REPORT OF EFSA

Modern methodologies and tools for human hazard assessment of chemicals[1]

European Food Safety Authority[2,3]

European Food Safety Authority (EFSA), Parma, Italy

*This scientific output, published on 11 July 2014, replaces the earlier version published on 24 April 2014**

ABSTRACT

This scientific report provides a review of modern methodologies and tools to depict toxicokinetic and toxicodynamic processes and their application for the human hazard assessment of chemicals. The application of these methods is illustrated with examples drawn from the literature and international efforts in the field. First, the concepts of mode of action/adverse outcome pathway are discussed together with their associated terminology and recent international developments dealing with human hazard assessment of chemicals. Then modern methodologies and tools are presented including *in vitro* systems, physiologically-based models, *in silico* tools and OMICs technologies at the level of DNA/RNA (transcriptomics), proteins (proteomics) and the whole metabolome (metabolomics). Future perspectives for the potential applications of these modern methodologies and tools in the context of prioritisation of chemicals, integrated test strategies and the future of risk assessment are discussed. The report concludes with recommendations for future work and research formulated from consultations of EFSA staff, expert Panels and other international organisations.

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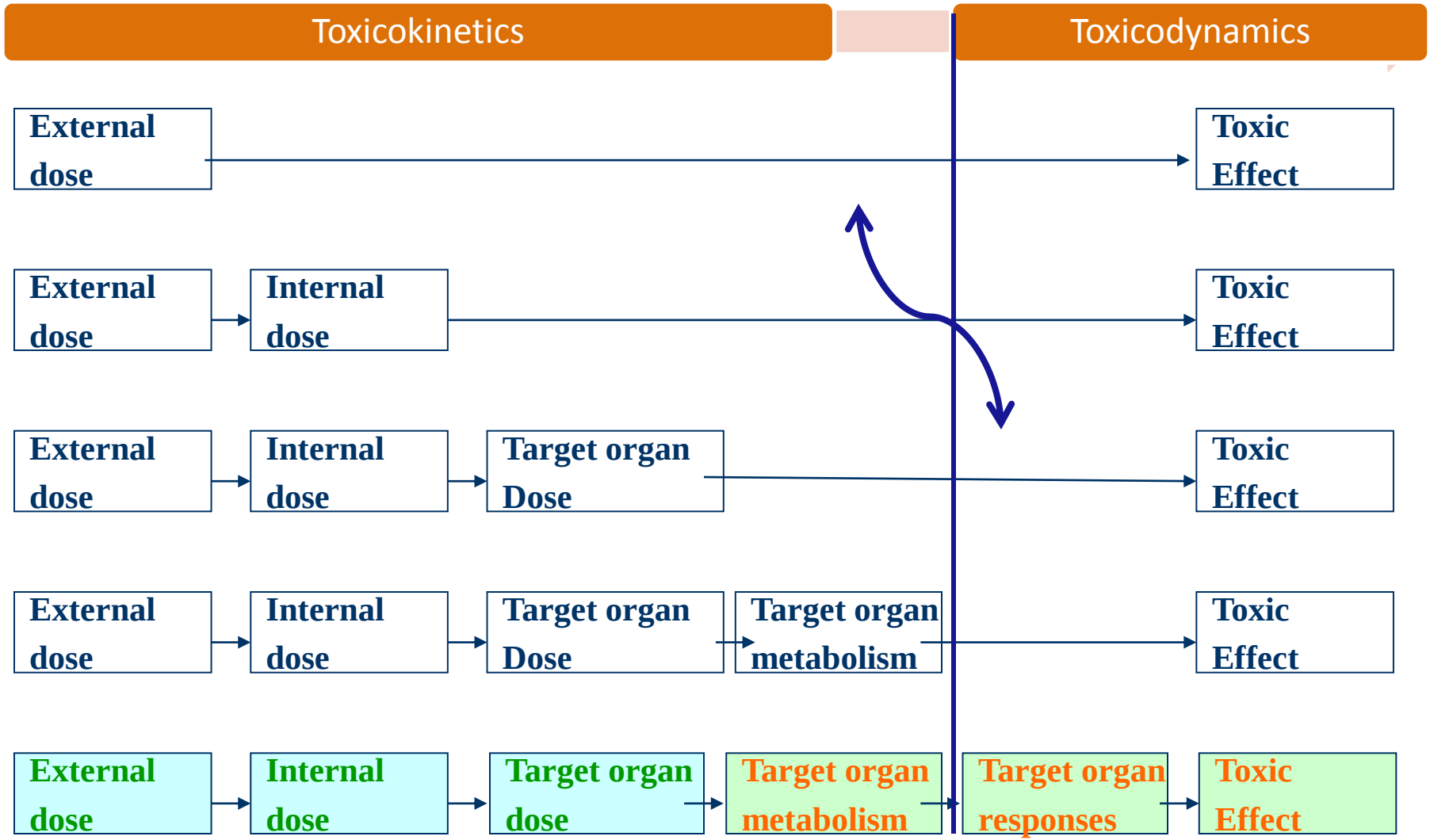
KEY WORDS

mode of action, adverse outcome pathway, integrated testing strategy, physiologically-based models, *in silico*, OMICs

-Levels of Knowledge, Toxicokinetic and Toxicodynamic processes



Biologically-based models: Integrating variability from Biological Processes in RA

TK AND MULTIPLE CHEMICALS : DATA AND MODELS

- **Integrating TK in Human, animal, environmental RA**

✓ Objective 1:

Review model/Tools in human, animal, Env RA (2016)

✓ Objective 2: Collect physiological/ biological parameters

- **Develop TK tools and models for single compounds** (from simple tools to generic PB-PK models).
- **Case studies 10 chemicals food/feed safety (2017)**

✓ Objective 3: **Develop TK tools and models for multiple chemicals** (from simple tools to generic PB-PK models).

- **Case studies 10 mixtures food/feed safety**

✓ **All tools in R Open sources EFSA website (2018)**

Data requirements for pesticides Regulation 283- 284/2013 : TK Data

In vivo TK studies in animals

Information blood/ tissues [C] for active substance/relevant metabolites on relevant species: understanding toxicity studies incl TK parameters ($C_{max;}$ AUC, T_{max})

Route/time course of excretion active substance and metabolites;

Investigating entero-hepatic circulation

Comparative animal versus human microsomes or intact cell systems

Relevance animal tox -guide interpretation, further define testing strategy. e.g. human *in vitro* metabolite not in test species

Protocols are available in the public domain (e.g. ECVAM and literature) incl. ECVAM work on developing TK standards

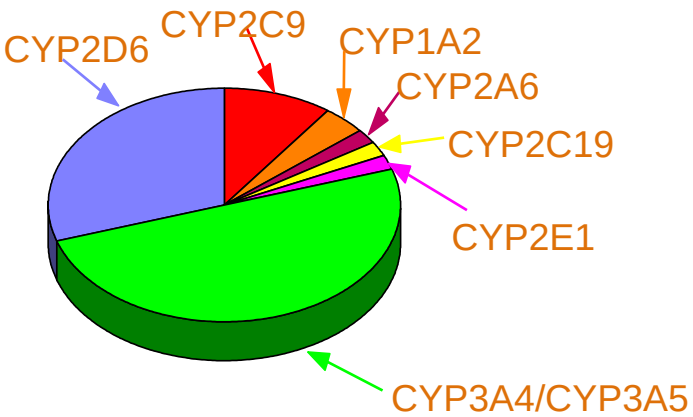
In vitro models hepatic and non-hepatic microsomes, e.g cDNA-expressed recombinant human CYPs, hepatocytes etc.

Major human metabolites (>10% of AD) not present at sufficient levels in animal studies further investigated for their toxicity profile.

MAJOR METABOLIC/EXCRETION ROUTES IN HUMANS

Phase I enzymes

Cytochrome P-450,
ADH, Esterases…



Phase II enzymes

Conjugation reactions

UDP-Glucuronyltransferases,
Sulphotransferases
Glutathione-s-transferases
Methyl-transferases
N-acetyltransferases
Amino acid conjugation

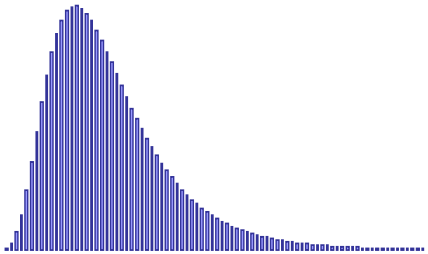
Transporters

Phase 0- Uptake transporters:
e.g OATPs, OCTs.

Phase III-Efflux pumps:
e.g ABCs (P-glycoproteins and MRPs)

Renal excretion

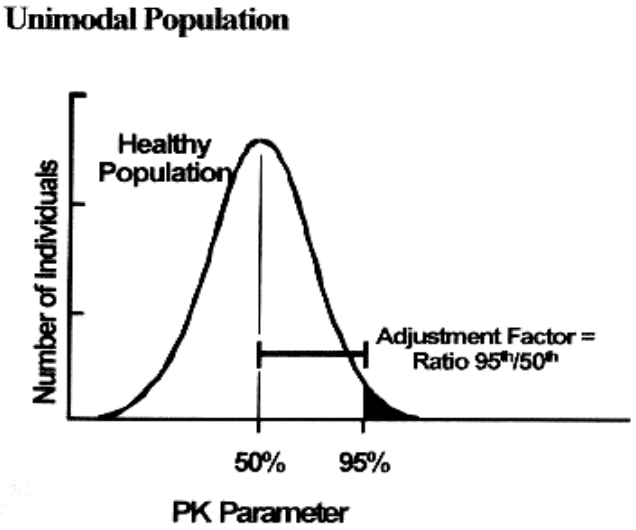
-HUMAN VARIABILITY IN TOXICOKINETICS -

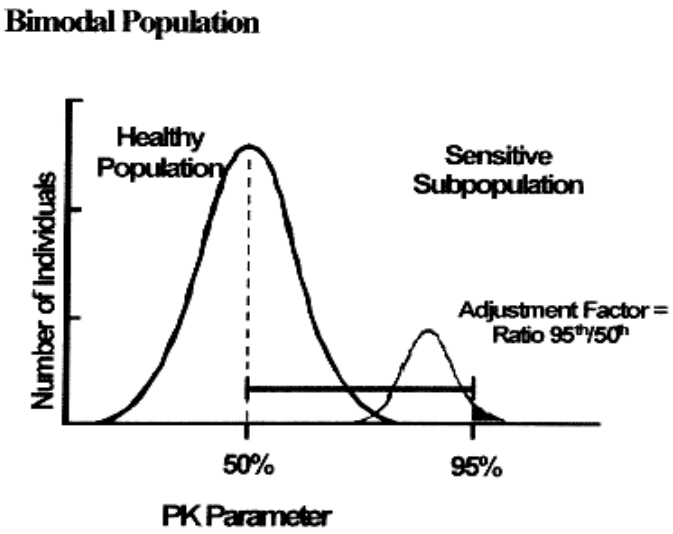


From pharmaceutical database human variability in TK available for many drugs /enzyme isoforms in different subgroups of the population.

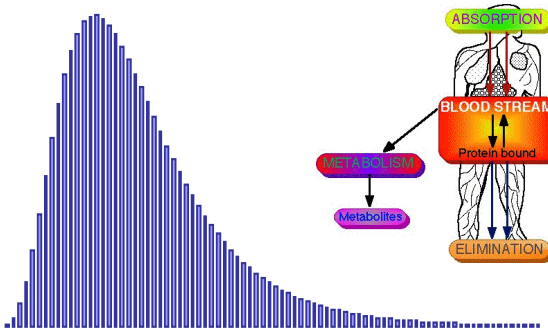
Rationale for meta-analysis of TK data to derive metabolism variability distributions

Can be combined with *in vitro* data and used in QIVIVE



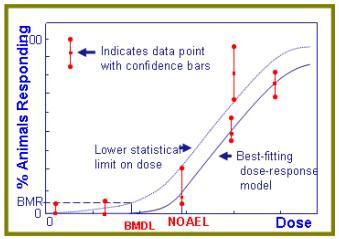


COMBINING VARIABILITY IN TK AND IN VITRO DATA : OPENSOURCE PLATEFORM



TK

TD



Isoform-specific Variability Distribution : Open Source Tool

Meta-analysis TK studies (acute, chronic)

Phase I (CYP), Phase II (UGT), Transporters etc…

Isoform-specific Metabolism

In Vitro Human cell system

Combine Human TK data and Tox data

Combine Human TK data and human epi data

Combine TK data and in vitro TD data

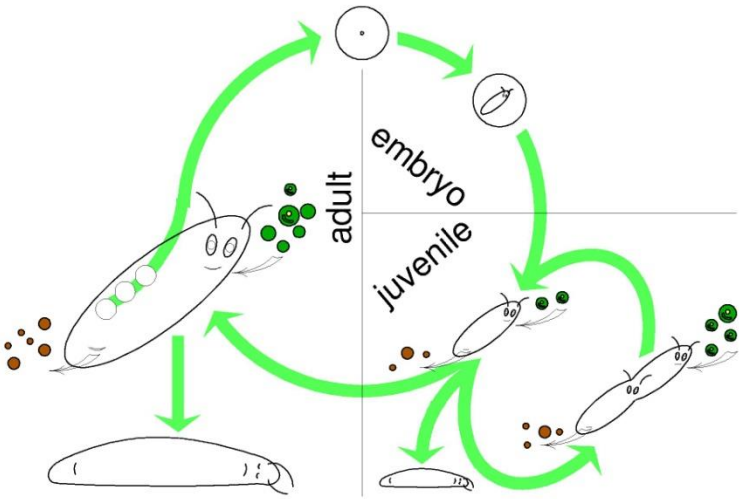
DEB MODELS

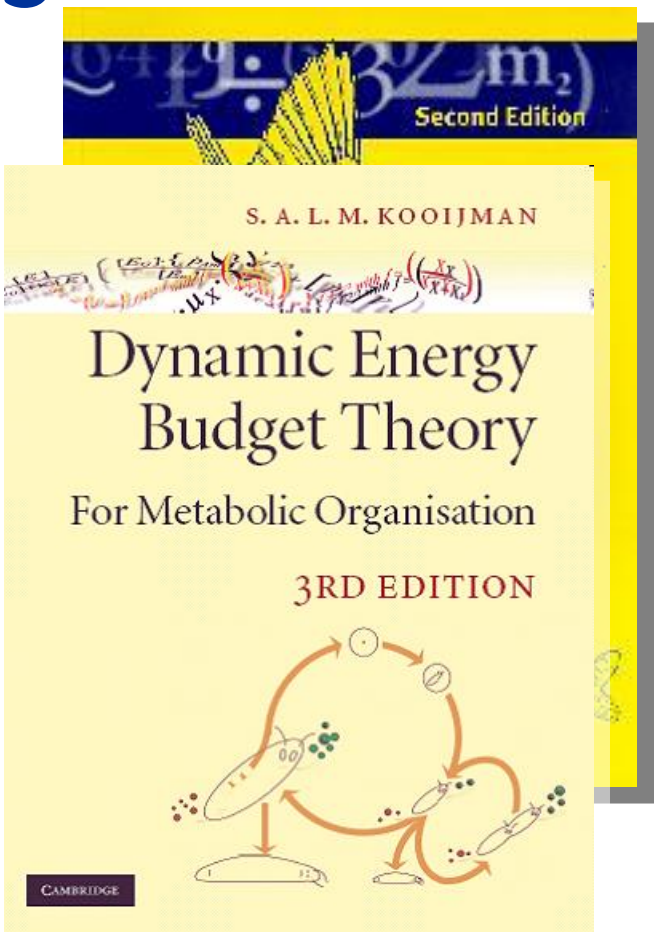
Quantitative theory for metabolic organisation from 'first principles'

- time, energy and mass balance

Life-cycle of the individual

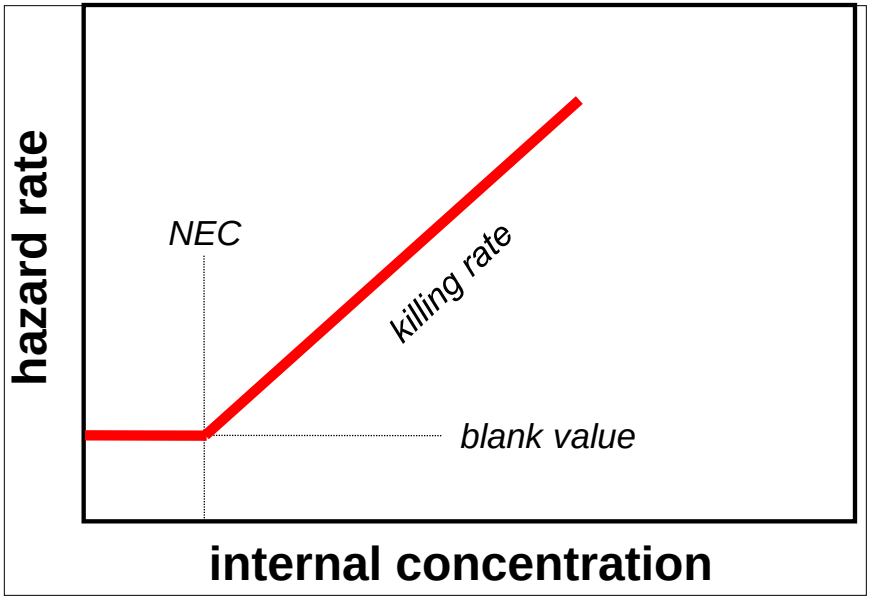
- links levels of organisation: molecule → ecosystems

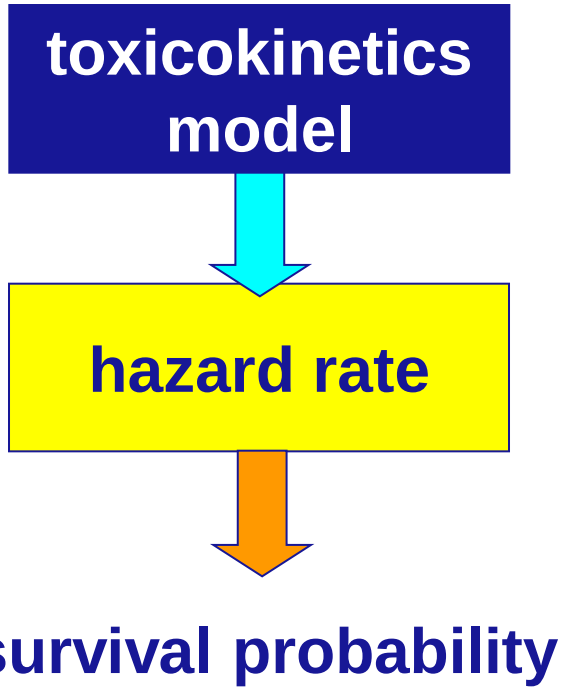




Kooijman (2010)

- Chemical affects the ***probability*** to die
  - hazard modelling





DYNAMIC ENERGY BUDGET MODELS FOR TERRESTRIAL AND AQUATIC ORGANISMS

- ✓ Objective 1: **Review DEB models** (**2016**)

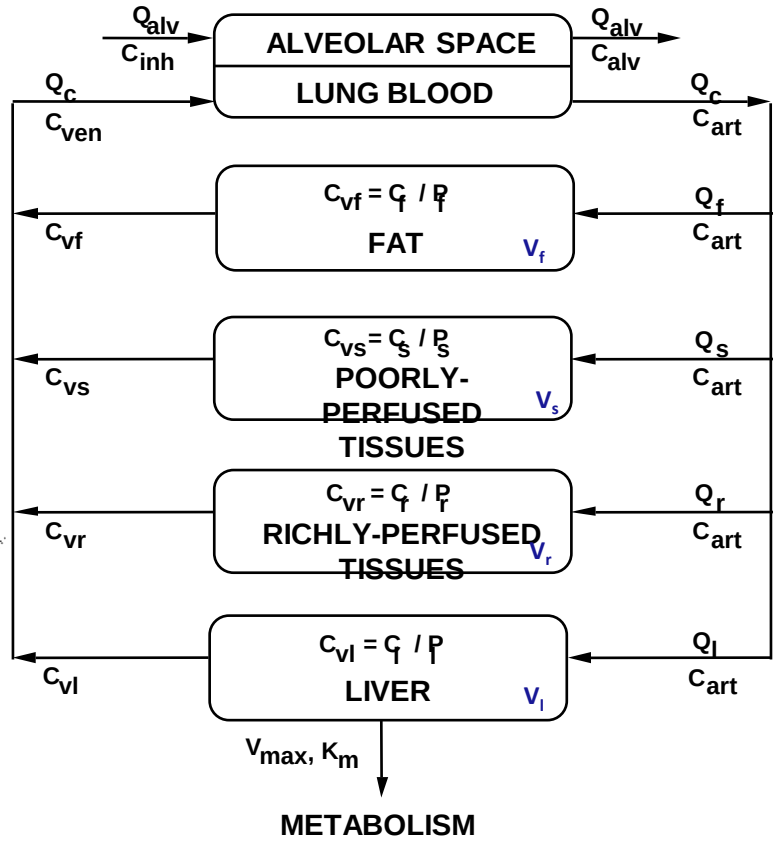
- ✓ Objective 2: **Collect physiological/ biological parameters-** calibration of models single compounds incl DEB (Spring 2017)
- Develop generic/specific models for aquatic and terrestrial organisms for single compounds-Endocrine case study

- ✓ Objective 3: **Develop tools and models for multiple chemicals** (Spring 2018).

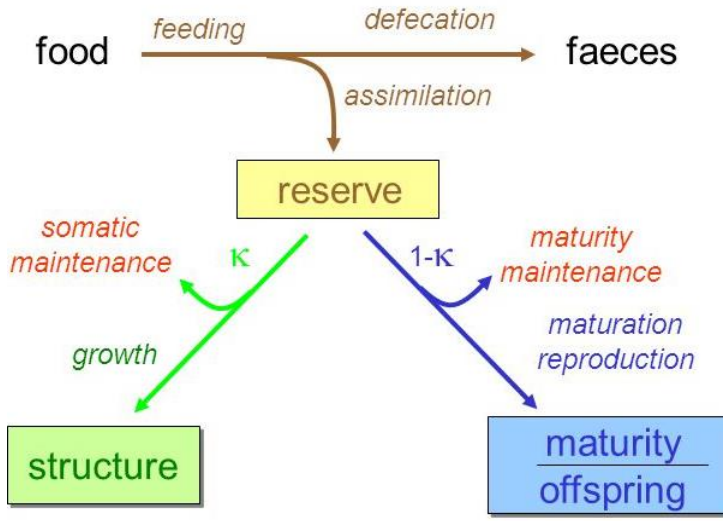
- ✓ **All tools in R and as Open sources on EFSA website**

-Building Open source TK and DEB tools-

External dose → Internal dose → Target organ dose → Target organ metabolism → Target organ responses → Toxic Response



PB-TK models



DEB Models

Future of TK data in Food Safety

- ✓ Open source Tools: TK Plate
- ✓ Further improve *in vitro TK*
- ✓ *In vitro* data and TK variability

From TK to full PB-TK

- ✓ Illustrate application of tools
- ✓ Tiered approaches/different contexts (e.g. data poor, data rich , mixtures)

Cooperation and Education

- ✓ Translate 21st century tools into practice
- ✓ Harmonised methods and tools
- ✓ Training current and next generation


Many Thanks
Questions ?